Alberta Heritage Foundation
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LIVING DONOR LIVER TRANSPLANTATION IN CHILDREN

Ann Scott

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Comments relative to the information in this paper are welcome and should be sent to:

Director, Health Technology Assessment Unit
Alberta Heritage Foundation for Medical Research
1500 10104 - 103 Avenue
Edmonton, AB T5J 4A7 CANADA
Tel: (780) 423-5727 Fax: (780) 429-3509
Web address: www.ahfmr.ab.ca
E-mail: info@ahfmr.ab.ca

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CONFLICT OF INTEREST

Conflict of interest is considered to be financial interest, either direct or indirect, that would be affected by the research contained in this report, or creation of a situation where an author's judgement could be unduly influenced by a secondary interest such as personal advancement.

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EXECUTIVE SUMMARY

Background

Liver transplantation is the definitive therapy for end stage liver disease in children. However, the number of cadaveric organs donated has remained relatively stable for many years, and the demand for cadaveric livers now far outstrips supply. Despite the development of innovative surgical techniques, such as reduced size liver transplantation (RSLT) and split liver transplantation (SLT), the donor graft deficit continues to grow. This has led to the search for new solutions, such as live donor liver transplantation (LDLT), which was first successfully performed in 1989.

Adult to child LDLT is now routinely offered in many Western countries. The purported advantages of LDLT include a shorter waiting time for a liver transplant; the ability to schedule the operation electively; reduced cold ischemic time for the donor liver; and increased availability of cadaver livers for patients still on the waiting list. There is also less likelihood of primary graft failure in the recipient since the graft is taken from a healthy, hemodynamically stable donor. However, donation of a liver graft is associated with up to 0.3% mortality and 3% to 17% morbidity. The risks incurred by LDLT donors, who are otherwise healthy, necessitate careful scrutiny of the safety and efficacy of LDLT.

Objectives

To evaluate the published evidence on the safety, efficacy, and current status of living donor liver transplantation for the treatment of end stage liver disease in children.

Methodology

Data were collected on children (< 18 years of age) undergoing liver transplantation for any indication. All original, published systematic reviews, comparative studies with at least ten patients in each study arm, or case series studies reporting outcomes for at least ten donors were identified by searching electronic literature databases and the web sites of various health technology assessment agencies, research registers, and guidelines sites from 1995 to June 2004. No language restriction was applied.

Results

Donors

The LDLT donor operation is lengthy but rarely results in the need for blood transfusion. On average, donors remain in hospital for at least five days. The mortality rate for live donors was 0.15%, and up to one in ten donors experience adverse effects ranging from bile leak and wound problems to more serious complications such as

small bowel obstruction. As many as 4% of donors will undergo another operative procedure because of complications related to LDLT.

Recipients

The overall patient and graft survival rates were similar for cadaveric whole liver transplantation and LDLT. There was no clear benefit conferred by either graft type with respect to vascular complications, bile leak, reoperation, or graft dysfunction. However, subgroup analysis of registry data suggested that LDLT resulted in significantly lower mortality and graft failure rates, compared to cadaveric whole grafts, in children younger than 2 years. The opposite was the case for children aged between 2 and 16 years.

Children undergoing RSLT generally fared worse than those who underwent LDLT. Graft and patient survival rates declined after RSLT over time and were much lower than those for LDLT at five years. RSLT recipients were also more likely to experience vascular complications.

LDLT produced better actuarial graft and patient survival rates at one year than SLT, but by five years there was no difference between the two graft types. The risk of experiencing graft dysfunction and bile leak or bleeding from the cut liver surface was similar for both procedures.

Conclusions and Recommendations

Despite its popularity, the evidence base for LDLT is incomplete. The current limited evidence suggests that LDLT is superior to all forms of cadaveric liver transplantation in children younger than two years of age. However, the safety and efficacy of LDLT was equivalent to, and in some cases worse than, SLT and whole liver cadaveric donation in older children. Despite its limitations, LDLT is a life saving procedure for some individuals where alternative transplant options are not available, such as for very small children or for elective patients whose condition is likely to deteriorate before a cadaveric graft becomes available.

It is unlikely that LDLT would be performed at centres where there is an abundant supply of cadaveric organs. Future initiatives in LDLT must aim to achieve minimal morbidity and zero mortality for donors. Programs performing LDLT must adhere to an extremely high standard of care that includes standard protocols for preoperative evaluation of potential donors and postoperative follow-up of both donors and recipients, as well as strong psychosocial evaluation and support programs.

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SCOPE OF THE PAPER

This response addressed a request from Alberta Health and Wellness. The objective of this Information Paper is to evaluate the published evidence on the safety, efficacy, and current status of living donor liver transplantation for the treatment of end stage liver disease in children.

BACKGROUND

The liver is one of the first organs to develop in a human embryo and is the largest internal organ of the body, weighing between 1.5 and 1.8 kilograms in an adult [1, 2]. It is a complex chemical factory that is essential to life. The liver processes fats, carbohydrates, and amino acids; makes essential proteins such as enzymes and blood clotting factors; stores fat soluble vitamins; produces bile; helps regulate blood cholesterol and glucose; assists in the control of various hormone systems; plays an essential role in immunological defence; and breaks down potentially toxic substances such as alcohol [1, 3, 4].

The liver is actually composed of eight autonomous segments that have their own separate blood supply and biliary channels; segments II to IV make up the left lobe, V to VIII make up the right lobe, and segment I forms the caudate lobe [1]. Blood enters the liver from the portal vein and hepatic artery and leaves via the hepatic veins [1].

Indications for Liver Transplantation in Children

End-stage liver disease (ESLD) occurs when functional liver cell mass falls below a critical level. Hepatic failure is either acute or chronic depending on the length of time it takes for the liver to fail. Acute exacerbation of an underlying chronic condition is referred to as acute-on-chronic hepatic failure. ESLD generally results from either obstruction of bile flow, known as cholestatic disease, or disruption of liver cell function. Hepatocellular diseases, such as viral hepatitis, cause liver tissue to become inflamed and necrotic, and typically result in a much faster clinical deterioration than cholestatic disease [5]. The failure of the ailing liver to perform its manifold functions leads to the build up of toxic substances in the body, and is associated with symptoms such as jaundice, muscle wasting, weight loss, bruising, collection of excess fluid in the peritoneal cavity, portal vein hypertension, hepatomegaly, reduced renal function, coagulopathy, and edema. Hepatic encephalopathy is another serious symptom that often occurs in patients with acute hepatic failure. It is characterised by disturbed brain function, which can manifest as personality changes, sleep disturbance, lethargy, lack of muscular coordination, and drowsiness. Severe hepatic encephalopathy results in coma and brain edema, which may cause brain stem herniation [5, 6]. ESLD is especially deleterious in children because it can retard growth and weight gain, impair cognitive development, and result in chronic malnourishment [7].

Biliary atresia is the most common cause of chronic cholestasis in children and affects one in every 8,000 to 12,000 infants [8]. It is an inflammatory process of unknown etiology that destroys the bile ducts, preventing bile outflow from the liver and eventually resulting in secondary biliary cirrhosis. Most children with untreated biliary atresia die from ESLD between 12 and 19 months of age, with fewer than 10% of children surviving beyond 36 months [7,8].

One option for children with biliary atresia is the Kasai procedure (or portoenterostomy), which is a surgical anastomosis between the bile duct remnant and a loop of the small intestine. Many consider the Kasai operation to be palliative because, even though it restores bile flow in up to 80% of infants when performed within the first three months of life, nearly three quarters of these children still develop recurrent cholestasis, portal hypertension, or cholangitis, and will eventually require a liver transplant [7-9]. Consequently, there is some doubt as to whether a Kasai operation should be performed prior to a liver transplant since it has a high failure rate and increases the technical difficulty of any subsequent operative procedure [10,11]. However, some studies have shown that performance of a prior Kasai operation does not influence patient or graft survival rates after transplantation [8,10]. Therefore, it is suggested that the Kasai operation may delay the onset of ESLD long enough to allow the child to grow, which not only helps the child survive the rigours of major surgery and reduces the technical difficulty of the transplant procedure, but also increases the chance of finding a size matched cadaveric donor graft [8,10,11].

Biliary atresia accounts for nearly half of all liver transplants performed in children younger than 18 years, and over 50% of transplants performed in children under five years of age [10,12,13]. Some of the other indications for liver transplantation in children include: metabolic disorders (urea cycle anomalies, alpha-1-antitrypsin deficiency, tyrosinemia, cystic fibrosis, glycogen storage disease, Wilson's disease); cryptogenic cirrhosis; familial cholestatic syndromes (Alagille's syndrome, Byler's disease); chronic hepatitis (hepatitis B, autoimmune chronic active hepatitis); primary sclerosing cholangitis; liver tumours such as hepatoblastoma; and fulminant liver failure [7,12,13].

Unlike patients with end stage renal disease who can survive with regular renal or peritoneal dialysis, there is currently no effective long-term mechanical or pharmaceutical replacement for a functioning liver. Consequently, the only curative treatment for ESLD is liver transplantation [14,15]. Pediatric liver transplants comprise 10% to 15% of all liver transplants performed in Western countries [11,16]. In 2003, just over 10% of the 359 liver transplants performed in Canada were for children younger than 18 years [13].

Liver Transplant Options

Cadaveric donor liver transplantation

The first human liver transplant was performed in the United States in 1963. While initial results were poor, subsequent advances in postoperative immunosuppressive regimens,

surgical technique, patient selection, and tissue preservation methods reversed this trend to the extent that liver transplantation is now considered to be the definitive therapy for ESLD [17].

The liver is the second most commonly transplanted human organ after the kidney [18, 19]. The main source of cadaveric livers in Western countries is brain dead donors with beating hearts [17, 20]. Once the cadaveric liver is removed, it is flushed with preserving solution and transported to the recipient's hospital. It then undergoes 'back table' preparation in which superfluous tissue is removed and vascular conduits are reconstructed. The recipient's diseased liver is then replaced with the donor liver, and the vascular and biliary connections are reconstructed [5, 21]. Graft rejection is controlled with an immunosuppressive regimen that must be continued for the rest of the patient's life [22, 23].

The approximate one, five, and ten year survival rate for pediatric recipients of cadaveric livers is 90%, 85%, and 75%, respectively, even though up to 20% of primary grafts fail [24-26]. Potential postoperative complications include graft rejection, liver dysfunction or failure, vascular and biliary problems, infection, and incisional hernia [5, 23, 27]. The prolonged immunosuppressive therapy can also result in diabetes, progressive renal insufficiency, hypertension, osteoporosis, post-transplant lymphoproliferative disorder, hypercholesterolemia, and malignancy [5, 28]. In children, the adjunctive use of corticosteroids in post-transplant immunosuppressive regimens can retard growth [23, 29].

The increasing prevalence of hepatitis C, combined with steady improvements in survival rates following liver transplantation, has caused a marked increase in the demand for liver transplantation. The pool of eligible transplant recipients has also been expanded by advances in surgical techniques [17, 30]. However, the number of cadaveric organs donated has remained relatively stable for many years, and demand for cadaveric livers now far outstrips supply [31, 32]. This organ shortage has been particularly grave for children because of the difficulty of finding size matched donors. In the 1980s, between 25% and 50% of North American children died while waiting for a transplant [33-36]. In an attempt to reduce the donor graft deficit, innovative surgical techniques were developed which exploit the liver's unique ability to regenerate rapidly and regulate its own growth and mass according to the optimum liver/body mass ratio required by the recipient [5, 37].

Reduced size liver transplantation

Reduced size (RSLT) or cut down liver transplantation was first described in 1984. The cadaveric liver graft from a larger child or adult is prepared ex situ on a back table to obtain either a left lateral segment (segments II to III) or a full left lobe (segments II to IV) that will fit the abdominal cavity of the recipient. The right hemi-liver used to be discarded [11, 33, 38], but it is now often transplanted into adult recipients. Over time, the liver graft reduces its mass via apoptosis, according to the needs of the recipient, and the abdominal wall stretches to accommodate the graft [39]. Occasionally, closure of the abdominal wall is delayed by temporarily interposing a prosthetic material in order to avoid complications, such as hepatic vascular thrombosis, respiratory compromise, and wound dehiscence, that may arise from high intra-abdominal pressure [40, 41].

One year patient and graft survival rates after RSLT vary from 62% to 78% and 47% to 62%, respectively, and are dependent on the condition of the recipient [42]. The survival rate of patients who electively undergo RSLT is similar to that of full cadaveric graft recipients [34]. However, RSLT does not make more cadaveric liver grafts available, it merely redistributes them. The result is increased competition between adult and pediatric recipients for the same small donor pool [34, 38]. This is particularly unhelpful given that the number of children on the waiting list for a liver transplant in the United States has more than doubled over the last ten years, while the number of adults has increased six fold [43]. Similar trends are evident in Canada [13]. Consequently, RSLT is now considered obsolete except in select circumstances, such as when the donor liver has sustained a focal injury [33, 39, 44] or there is only one potential recipient who requires a reduced sized graft.

Split liver transplantation

The first successful split liver transplant (SLT) was reported in 1989. SLT was a new innovation designed to expand the pool of cadaveric liver grafts [38]. It typically involves splitting the cadaveric liver after it is removed from the donor (ex situ SLT) to yield one right lobe graft, usually for an adult recipient, and one left lateral segment or left lobe graft for a child [37, 42]. A challenge of SLT is ensuring that the graft provides sufficient functional liver mass for both recipients [45]. In general, a cadaveric graft should be at least 40% of the size of the recipient's normal liver volume or at least 1% of the recipient's body weight [33, 41, 45]. The liver graft volume doubles in the recipient within seven days and is almost completely regenerated by 60 days post-transplant [37, 46]. The patient and graft survival rates for pediatric SLT are approximately 75% and 59%, respectively, and are dependent on the condition of the recipient [47]. Initial results were inferior to cadaveric whole organ and reduced size transplants largely because of the technical complexity of SLT, its inappropriate use in urgent cases, and the lengthy back table manipulation which exposed the graft to prolonged cold ischemia and potential rewarming [12, 33, 48]. In situ SLT was subsequently developed in 1995, and involves splitting the liver while it is still in the beating heart donor. This reduces cold ischemic time; makes it easier to identify biliary and vascular structures; enables detection of bile leaks or bleeding from the cut surface

of the graft; eliminates the danger of graft rewarming; and leaves the right liver lobe intact and undisturbed [11, 33, 38]. With experience, similar outcomes can be achieved with in situ and ex situ SLT, but debate continues over which technique is best [38]. The survival rate of children receiving a split liver graft is comparable to those receiving a cadaveric whole liver graft [42, 49].

Although conceptually attractive, various technical, logistic, and organ allocation policy issues have stymied the widespread use of SLT to the extent that it comprises less than 2% of all liver transplant procedures in North America [5, 40, 46]. Achieving an adequately sized left lobe graft can compromise the function of the right lobe graft [4, 36]. In situ SLT also lengthens the graft harvesting procedure by at least an hour, which potentially jeopardises the retrieval of other thoracic organs from multiorgan donors [33, 45, 48, 50]. In addition, the procedure is both labour and resource intensive. Careful donor selection is crucial to the success of SLT since two recipients are potentially at risk of primary graft dysfunction. Consequently, donor selection criteria are typically conservative, which means that only 15% to 25% of cadaveric donor livers are suitable for splitting [33, 35, 44].

Living donor liver transplants

In Canada, 30 children required a liver transplant at the end of 2003; six children had already died waiting for one [13]. Many children also die when their condition deteriorates to the point that they are no longer eligible to receive a transplant [51]. The chronic donor liver shortage in most Western countries led to the search for new solutions, such as live donor liver transplantation (LDLT).

LDLT was first successfully performed in 1989 [36, 51]. It originally involved transplanting the left lateral liver lobe of an adult into a child, but the technique was soon extended to transplantation of the larger right lobe into adult recipients [20, 36, 51]. Adult to child LDLT generally involves resection of either a left lateral segment, which represents between 15% and 20% of the donor's total liver mass, or a full left lobe, which is 30% to 35% of the donor's total liver mass, from a parent or family member [34, 42].

In LDLT a balance must be struck between providing the recipient with sufficient functional liver cell mass to survive and ensuring an adequate residual liver volume in the donor. It is generally accepted that the donor hepatectomy should not exceed 70% of the total liver mass [52]. The graft should be at least 30% of the size of the recipient's normal liver volume or at least 0.8% of the recipient's body weight [15, 52, 53]. However, these ratios are dependent on the recipient's condition, the quality of the graft, and the implantation technique [54]. The small size of left liver lobe grafts limits their use to recipients weighing less than 60 kilograms. Consequently, left liver lobes comprise the majority of grafts used in pediatric LDLT [55].

In LDLT the liver segment is usually dissected without disrupting the blood flow to the liver, and blood transfusions are not normally required [33]. The liver graft is then removed from the living donor, flushed with cold preserving solution, and prepared for transplantation. The

divided vessels in the donor are then over sewn. The recipient operation is similar to SLT except that the donor and recipient operations are usually performed in adjacent operating rooms to minimise the cold ischemic time of the liver graft [34, 56]. However, removal of the diseased liver can be laborious in children who have had previous upper abdominal surgery, such as a Kasai operation, because of dense adhesions that have often become vascularised due to portal hypertension [56].

Adult to child LDLT is now routinely offered in many Western countries. The number of live transplants performed in the United States increased markedly from 56 procedures in 1996 to 509 in 2001, whereas the number of cadaveric transplants remained stable [14, 32, 51]. Similarly, 13% of all liver transplants performed in Canada in 2002 involved live donors [31]. Initially, most LDLT procedures were performed in children, but now the majority is adult to adult LDLT. Of the 39 pediatric liver transplants conducted in Canada in 2003, 82% were cadaveric and the remainder were live donation [13].

Potential advantages and complications

The purported advantages of LDLT include a shorter waiting time for a liver transplant; the ability to schedule the operation electively and optimise the recipient's condition prior to transplantation; the option of performing a pre-transplantation cross match between donor and recipient; reduced cold ischemic time for the donor liver (from over 8 hours for a cadaveric liver to less than one hour for a live graft); and increased availability of cadaver livers for the patients still on the waiting list. Also, there is less likelihood of primary graft failure in the recipient since the graft is taken from a healthy, hemodynamically stable donor rather than from a donor who has just died from trauma or illness [15, 30, 51, 52, 54].

The range of complications experienced by LDLT recipients is similar to those associated with cadaveric graft procedures. However, LDLT has its own inherent problems. Like SLT, the biliary and vascular anastomoses in LDLT are technically more difficult to perform than for whole organ transplantation, which increases the risk of biliary leaks, vascular thrombosis, and pulmonary embolism [30, 51, 56, 57]. Small infants, especially those who are chronically ill and malnourished, have a particularly high risk of developing postoperative complications, compared to older children and adolescents [7].

Donation of a left lateral segment or full left lobe is associated with 0.1% to 0.3% mortality and 3% to 17% morbidity, whereas the risk of right lobe donation is far higher [42, 54, 58, 59]. In comparison, living kidney donors have a mortality risk of 0.03%, a 2% risk of major morbidity, and a 10% to 20% risk of minor morbidity [20]. Perioperative morbidity for live liver donors can include hepatic insufficiency or failure, portal vein thrombosis, deep vein thrombosis, bleeding, a need for blood transfusion, bile duct injury, bile leak, abscess, wound infection, gastroduodenal ulcers, incision pain, hernia, splenic injury, and late intestinal obstruction due to adhesions [60-62].

EVIDENCE FOR THE USE OF LDLT IN CHILDREN

A summary of extracted data from selected studies is tabulated in Appendix A. The search strategy and study selection criteria are outlined in Appendices B and C.

Safety and Efficacy/Effectiveness

Donor outcomes

To date, a systematic review of donor outcomes after adult to child LDLT has not been published. A number of case series studies have been published, but many of these were excluded because either the ages of those receiving the donated liver grafts were not specified or the donor results from adult to adult and adult to child LDLT were pooled.

Fourteen studies were identified that reported outcomes for 712 people who donated a portion of their liver to a child younger than 18 years. As expected, the majority of donors were either a parent of the child or a close relative, and the left lateral segment was the most commonly donated liver graft. In four studies [62-65] the average age of the donors was around thirty years, while three studies [41, 66, 67] reported donor age ranging from 19 to 54 years. This age profile probably reflects both the donor selection policy of the individual clinics and the fact that parents are the main source of donated liver grafts for pediatric recipients. Length of follow-up was reported by five studies [41, 65, 66, 68, 69] and only extended beyond a year in two of them. The median study period for thirteen of the fourteen studies was five and a half years.

The majority of the studies reported donor assessment as a step wise process that generally started with a medical history and routine biochemical evaluation of blood, followed by, or in conjunction with, psychosocial and psychiatric assessment. Donors who were still eligible then underwent computed tomography, magnetic resonance imaging, and/or ultrasonography to determine the anatomy and volume of their liver. Four studies [41, 67-69] reported that 25% to 73% of potential donors were ineligible to donate for medical or surgical reasons. Of the five studies that reported using cholangiography to assess biliary anatomy, four [62, 64, 68, 70] used it routinely and one [69] used it only in select patients. Similarly, four [62, 67-69] out of six studies routinely used angiography. One study [41] used it selectively, whereas the remaining study [66] abandoned angiography in favour of Doppler ultrasound examination early in the patient series because of the serious complications potentially associated with it. Only one study [67] reported performing liver biopsy as part of the preoperative donor assessment. Biopsy was performed in 25 patients, 15 of whom did not go on to donate a liver graft.

The mean length of time for the graft procurement procedure ranged from just under four to over six hours. Few donors required blood transfusion, except for one study [69] in which over half the donors received an autologous transfusion. The average hospital stay ranged from 5 to nearly 14 days; the longest stay for a single patient was 34 days. However, no perioperative complications were reported. One postoperative death was reported in a donor who had three

major risk factors, and the authors of the study stated that in retrospect the person should not have been accepted as a donor [69]. The most commonly reported postoperative complications were bile leak (0% to 10%), incisional hernia (approximately 6%), gastroduodenal ulcer (1% to 6%), and wound infection (2% to 6%). One study [68] reported that 4% of donors required reoperation to rectify postoperative complications resulting from LDLT. However, most of the studies did not report the length of follow-up, which makes the data difficult to interpret.

Nearly 72% of donors reported attaining pre-donation status in less than three months after LDLT in one study [66]. However, little or no information was provided by the other studies on the length of time required for donors to fully recuperate after LDLT. One study conducted a postoperative survey of 60% of the donors to assess psychological wellbeing, though it was not clear why only a subset of the original donor group was surveyed. The results showed that 37% of surveyed donors had increased self confidence; 55% felt privileged to have had the opportunity to donate a liver graft; and 55% expressed pride in being a donor and reported closer links within their family as a result of the donation. In addition, 29% of donors experienced transitory depression, while 34% experienced feelings of exaltation. It is notable that mostly the same patients were reporting these contrasting emotions. All the donors felt that they had made the right choice and would donate again, and 92% said that they would encourage others to donate a liver graft [41]. The survey was conducted over an extended follow-up period that ranged from less than six months to over two years.

One study [65] used in-depth interviews with parents to assess quality of life issues following the donation of a liver graft to their child. Despite the safeguard of a multi-step informed consent process that involved a donor advocate and a cooling off period, 93% of donors stated that their decision to donate was not objective. Many felt that once they were identified as a suitable donor they no longer had free choice in the decision. However, none of the donors regretted their decision to donate irrespective of whether the transplant was successful or not. Two thirds of the donors felt that they were regarded as non-patients by the medical team, particularly with respect to postoperative treatment of pain and long-term follow-up care, which were largely considered to be inadequate. Even though family relationships were generally strengthened by the donation experience, most donors experienced financial strain following donation, particularly with respect to non-medical costs, such as travel, child care, and lost income, that were not covered by medical insurance.

Recipient outcomes

Some of the included studies reported other comparison groups that are not listed in Appendix A because they comprised pooled data from different graft types, most commonly reduced and split liver grafts. For example, if a study reported outcomes for whole liver transplantation, LDLT, and a combined group of RSLT and SLT recipients, only the data for whole liver transplantation and LDLT were extracted.

Cadaveric whole organ graft versus LDLT

Eight studies with a median study period of 11.5 years compared cadaveric whole organ grafts with LDLT. The mean cold ischemic time of the liver graft was shorter by an average of 432 minutes in one study [45]. Actuarial survival rates for patients receiving cadaveric grafts were similar for both procedures at six months. However, after one year, and extending up to five years, the survival rate was a little higher in the LDLT group (median five year patient survival rate was 92% for LDLT and 81% for cadaveric whole organ grafts). This was also true for graft survival rates (median five year rate was 81% for LDLT and 73% for cadaveric whole organ grafts). There was no discernible difference between the two graft types with respect to reoperation or primary graft non-function rate. In terms of safety, one study [71] found that cadaveric whole grafts were more likely to have hepatic artery outflow complications, such as thrombosis, while another study reported similar rates of these problems between the two treatment groups [45]. Two studies [45, 57] reported higher rates of portal vein complications after LDLT, but another study [71] observed the opposite. There was no obvious difference between the two graft types with respect to biliary or hepatic vein complications.

Two studies [72, 73] reported analyses of data derived from the Organ Procurement and Transplantation Network registry, which is administered by the United Network for Organ Sharing (UNOS) in the United States. One study [72] tracked over 3,800 children who had received a primary liver graft. Children between 0 and 2 years of age who underwent LDLT had a 30% lower risk of graft failure compared to those who received a cadaveric whole liver graft ($p = 0.02$), but there was no difference in mortality between the two groups ($p = 0.66$). However, children older than 2 years had higher graft failure rates after LDLT than cadaveric whole organ liver transplantation (age 2 to 10 years, $p = 0.02$; age 11 to 16 years, $p = 0.0001$). The risk of death was also higher after LDLT in the 2 to 10 year age group ($p = 0.02$), whereas the risk was similar between the two groups for older children. Three years after the transplant operation, the graft and patient survival rates were similar for both LDLT and cadaveric whole liver grafts. There was no difference in patient outcomes when the data were analysed with respect to the extent of the transplant centre's experience with liver transplantation. The authors concluded that the quality of the donor organ has a significant effect on recipient recovery within the first year after transplantation, but that subsequent outcomes are influenced by factors other than the type of graft received [72].

The second registry data study [73] analysed data from over 3,400 children who had received a liver transplant. While this study shared a common core of patients with Roberts et al. [72], the inclusion criteria were slightly different; it included children from a wider age range as well those who had undergone repeat liver transplantation. There was no difference in one year patient or graft survival rates between cadaveric whole organ and live liver grafts. However, a subgroup analysis of patients younger than one year showed that patient and graft outcomes after LDLT were superior to cadaveric whole liver grafts ($p < 0.002$). It was noted that LDLT was more likely to be performed as an elective procedure in stable patients who were undergoing liver transplantation for the first time [73].

Reduced size cadaveric graft versus LDLT

Five studies with a median study period of 11.6 years compared RSLT with LDLT. Liver grafts experienced a much longer total ischemic time during RSLT than LDLT [74]. Patient survival rates were similar between the two groups at three months, whereas the graft survival rate was much higher in LDLT recipients at three months [74]. Actuarial patient and graft survival rates were much lower after RSLT at one and five years, compared to LDLT (median five year patient survival rate was 92% for LDLT and 65% for RSLT; median graft survival rate was 81% for LDLT and 63% for RSLT). There was no discernible difference between RSLT and LDLT in terms of acute graft rejection. Vascular complications involving the hepatic artery and portal vein were more likely to occur after RSLT than LDLT.

Registry data [73] showed that one year patient ($p = 0.001$) and graft survival ($p = 0.007$) rates were significantly lower after RSLT than LDLT. This difference was sustained for graft survival after the exclusion of patients who were undergoing re-transplantation or who were in the intensive care unit at the time of transplantation, but not for patient survival. A subgroup analysis of patients younger than one year showed that patient and graft outcomes after LDLT were superior to RSLT ($p = 0.001$). It was noted that over half of the children who were hospitalised or in intensive care at the time of transplantation received a reduced size graft.

Split liver cadaveric graft versus LDLT

Five studies with a median study period of nearly 14 years compared SLT with LDLT. On average, the transplantation procedure was one hour longer for LDLT than SLT, but the mean cold ischemic time for the graft was much shorter during LDLT [63]. One study reported similar patient and graft survival rates at six months between the two groups, but higher survival rates after LDLT at one year [16]. Actuarial patient and graft survival rates were similar after five years (median five year patient survival rate was 92% for LDLT and 88% for SLT; median graft survival rate was 81% for LDLT and 79% for SLT). One study reported a strong trend toward increased primary graft non-function after SLT, but this was not statistically significant [16]. Another study found no discernible difference between the two procedures [63]. The risk of blood loss, acute graft rejection, re-transplantation, biliary and vascular complications, bowel perforation, and bleeding from the cut surface of the graft was similar for both groups.

Registry data [73] showed that one year graft survival rates were significantly lower after SLT than LDLT ($p = 0.001$), whereas patient survival rates were comparable. The differences in graft survival rates were not affected by the exclusion of patients who were sicker at the time of transplantation.

CLINICAL PRACTICE GUIDELINES AND POSITION STATEMENTS

The Live Organ Donor Consensus Group was sponsored by the National Kidney Foundation and the American Societies of Transplantation, Transplant Surgeons, and Nephrology to evaluate the current practice of live donor organ transplantation [75]. A national consensus conference was convened to establish practice guidelines that address the social, ethical, and medical aspects of donors participating in live donor organ transplantation. The central tenet of the document is that the health and safety of the donor should be paramount when considering LDLT. Donors should be healthy, of legal age, have an emotional relationship with the recipient, be willing and able to comply with long-term follow-up, and have sufficient intellectual capacity to give informed consent. Evaluation of donors must be undertaken by a multidisciplinary team. This should incorporate an assessment to ensure that donors fully understand the procedure, and its associated risks, and are not coerced. The recipient should be medically suitable according to standard criteria and must understand the risk incurred by the donor. LDLT should not be performed when the recipient has a poor chance of survival. The Consensus Group suggested that a government funded national registry of donor outcomes should be established.

EXPERT OPINION

Expert opinion was obtained from a transplant physician in Ontario who has expertise in LDLT. Since there are many causes of ESLD, there is no single standard treatment for this illness. The management of children prior to transplantation is aimed at treating symptoms and maintaining their health by promoting proper nutrition and vitamin supplementation, and completing immunisation protocols. In Canada, LDLT is an optional treatment for ESLD that is neither experimental nor standard of care. However, debate continues over the ethics of offering LDLT. Some centres navigate a middle ground by offering LDLT as a last resort when it is clear that the child's condition is deteriorating and a suitable cadaveric donor is unlikely to be found in time. In such cases, LDLT is offered only after a thorough discussion of the risks involved, and an alternative, such as SLT, is provided whenever possible.

The indications for LDLT in children are the same as for cadaveric liver transplantation. However, the children that benefit most from LDLT are those who are unlikely to survive long enough to receive a cadaveric organ. Some centres in Canada also offer LDLT to patients with fulminant liver failure, despite the continued controversy over whether truly informed consent can be obtained from the donor in such an urgent situation.

All candidates for LDLT can be successfully treated with cadaveric donor grafts. In the expert's opinion, LDLT offers no advantage over cadaveric grafts in terms of long-term survival, and the outcomes of those receiving a cadaveric whole organ graft appear to be slightly better than for LDLT recipients [76]. In fact, UNOS has now adopted a policy whereby all pediatric donor organs must go preferentially to pediatric recipients due to the better outcomes obtained with whole organ grafts. However, the supply of cadaveric donor organs falls far short of demand. LDLT provides the opportunity of performing the procedure electively and gives parental donors the chance to be active in their child's treatment. Many programs in Canada now perform more adult to adult LDLT than adult to child LDLT because of the substantial number of adults who die while waiting for a cadaveric organ. In contrast, SLT is becoming more common to the extent that some transplant units in Canada now rarely perform adult to child LDLT. It is likely that the majority of transplant surgeons in Canada would prefer to see efforts directed at increasing the number of available cadaveric organs rather than an expansion of LDLT.

ONGOING RESEARCH

In 1995, a group of physicians and surgeons established Studies of Pediatric Liver Transplantation (SPLIT), which is a privately sponsored cooperative effort between American and Canadian transplant centres [77]. SPLIT aims to prospectively collect and analyse data on at least 80% of all pediatric liver transplants performed in North America. Participation in SPLIT is open to all transplant centres conducting pediatric liver transplantation, and currently 39 transplant centres voluntarily submit data. The SPLIT initiative intends to quantify patient and

graft survival, and morbidity rates; identify potential prognostic factors; characterise immunosuppressive therapy and its side effects; analyse the incidence, risk factors, treatment, and outcome of Epstein-Barr virus infection and lymphoproliferative disease; and ascertain how the growth of children is affected by liver transplantation and immunosuppression.

The Canadian Council for Donation and Transplantation is currently conducting a Live Organ Donation Survey to identify the policies, practices, experiences, and perceptions related to live organ donation in Canada. A range of stakeholder perspectives will be canvassed including those of government, non-profit organisations, donation programs, health professionals, and donors. The report is scheduled for release in June 2004.

DISCUSSION

Safety and Efficacy/Effectiveness of LDLT in Children

Donors

Donors participating in adult to child LDLT are usually a parent of the recipient, and are generally young. The donor operation is lengthy but rarely results in the need for blood transfusion. On average, donors remain in hospital for at least five days. The mortality rate for live donors was 0.15%, and up to one in ten donors experience adverse effects ranging from bile leak and wound problems to more serious complications such as small bowel obstruction. As many as 4% of donors will undergo another operative procedure because of complications related to LDLT. However, in the two studies that reported postoperative psychological wellbeing, all donors said that they would donate again [41, 65].

Generally, donor evaluation is a step wise process that assesses donors for overall health, blood group compatibility, and any underlying anatomical or medical condition that may preclude donation. The donor then undergoes psychosocial evaluation to confirm informed consent and ensure that the decision to donate is free of coercion. Up to three quarters of potential donors may be ineligible to donate for medical or surgical reasons. A number of studies reported the routine use of cholangiography and angiography in assessing donor anatomy. The morbidity resulting from these techniques was not reported, even though it is particularly pertinent for potential donors who do not eventually donate. Only one study reported on aborted donor operations, which occurred in two instances; one procedure was stopped prior to hepatic dissection while the other was halted only after graft removal [70]. One study [65] that qualitatively assessed postoperative quality of life issues in donors highlighted the need to provide financial counselling and more information to donors on the long-term effects of donation prior to the procedure; include postoperative follow-up of the physical and psychological health of donors in transplant programs; and assign a medical team member to the donor in the postoperative period who is independent of the team caring for the recipient.

The true incidence of morbidity and mortality for donors providing liver grafts to children is unknown because many studies include results from a contingent of adults who have donated a left or right liver lobe to another adult. Consequently, while the studies included in this report represent a pure subset of the results reported for people who have donated liver grafts to recipients under the age of 18 years, they are nonetheless only a subset. In addition, the donor assessment protocol is rarely reported in detail, so it is impossible to tell if morbidity occurs as a result of this evaluation process. There is significant variability between centres in their post-operative follow-up of donors, and up to a third do not have a formal donor follow-up protocol [78]. The comprehensiveness of these protocols is often diverse and many programs do not systematically track donor complications over time. In fact, most of the included studies did not report the length of the follow-up period, which made the results very difficult to interpret. The evidence base also suffers from the absence of a clear definition of what constitutes an adverse effect after liver transplantation. Thus, the data currently available on donor outcomes is far from complete.

Recipients

Despite the significantly longer ischemic time experienced by cadaveric whole liver grafts, compared to live grafts, the overall patient and graft survival rates were similar between the two groups. In terms of complications, there was no clear benefit conferred by either graft type with respect to vascular complications, bile leak, reoperation, or graft dysfunction. However, subgroup analysis of registry data suggested that LDLT resulted in significantly lower mortality and graft failure rates, compared to cadaveric whole grafts, in children younger than 2 years. The opposite proved to be the case for children aged between 2 and 16 years.

Children of any age undergoing RSLT generally fared worse than those who underwent LDLT. Graft and patient survival rates declined after RSLT over time and were much lower than those for LDLT at five years. RSLT recipients were also more likely to experience vascular complications.

LDLT produced better actuarial graft and patient survival rates at one year than SLT, but by five years there was no difference between the two graft types. The risk of experiencing graft dysfunction and other commonly reported complications of segmental graft transplantation, such as bile leak and bleeding from the cut liver surface, was similar for both procedures.

The assessment of LDLT is problematic because of limitations inherent in the evidence base. The outcomes reported were very heterogeneous, making it difficult to establish a comprehensive profile of patient outcomes. Duplicate publications were also common, which increases the chance of double counting the data. The ethical imperative of wisely using a liver graft from a living donor means that LDLT is usually performed in recipients who are specifically chosen as having the best chance of a favourable outcome. Consequently, direct comparisons between these elective patients and the recipients of RSLT and SLT who are more likely to undergo emergency transplantation and are generally sicker at the time of surgery can

be misleading [51]. Many of the included studies provided only scant baseline patient information, so it was unclear if confounding prognostic factors, such as age, indication for transplant, UNOS status, and prior transplant surgery, were evenly distributed between the treatment groups. This was particularly true for the registry data. The variability in surgical technique, operative skill, and postoperative management among transplant centres also limits intra- and inter-study comparisons [79]. For example, patient survival rates can be greatly influenced by how aggressively the transplant centre pursues re-transplantation in children with signs of early graft failure [63].

The study period of the majority of the studies spanned more than a decade, which can bias the results because of changes in surgical technique and postoperative patient management, particularly the immunosuppressive regimens, that inevitably occur over such a long period of time. Also, most of the studies included their first experiences with LDLT, which are much more recent than for the cadaveric transplant techniques, and this introduces confounding from the learning curve effect. This was clearly demonstrated in the studies that analysed their results according to eras of transplantation [57, 71]. Recipient follow-up was generally short, particularly for LDLT because of its more recent introduction, which is a significant flaw. Long-term follow-up is especially important in pediatric patients because they are likely to live for many decades after transplantation.

Controversial Aspects

The main impetus for developing LDLT was to offset the shortage of cadaveric organs rather than to overcome shortcomings in the cadaveric transplant procedure [80, 81]. In fact, transplanting a segmental graft from a living donor is more technically challenging than the implantation of a full sized liver from a cadaveric donor [54]. Therefore, any advantage conferred by LDLT with respect to better organ quality and shorter ischemic time is potentially offset by the technical disadvantages. Similarly, the longer graft ischemic time of SLT is counterbalanced by the extra time required for the recipient procedure in LDLT [63]. Early synthetic function in LDLT grafts appears to be better than in SLT grafts, but the latter recover soon after transplantation. However, it is unclear if these differences in early injury have any detrimental effects on long-term graft
function [63].

The purported immunologic al advantage of LDLT over cadaveric grafts is debatable because data on rejection rates are equivocal [82]. This has important implications for children because exposing them to long-term immunosuppression, which is associated with serious side effects such as growth retardation and an increased risk of developing cancer, is far from ideal [11, 29]. Consequently, many centres continue to tinker with the composition of immunosuppressive regimens in an effort to find one that prevents rejection but has minimal side effects. Some centres have been able to reduce immunosuppression in children, or even wean long-term transplant survivors from it completely. However, there is currently no way of identifying

which children have developed graft acceptance to an extent that would allow the tapering of immunosuppression [11].

Indications for accepting recipients for LDLT remain controversial. The determination of suitability for transplant is based on an assessment of the severity of liver failure, the prognosis of the patient with current medical/surgical therapy, the patient's current quality of life, and the potential of the transplant to restore the patient's health [17]. LDLT is particularly suited for children who are still in generally good condition and have a reasonable chance of a favourable outcome, but who are at high risk of rapid deterioration or a long wait for a cadaveric transplant [54, 84]. In the United States and Europe, there is general agreement that live donation should only be offered to patients who meet the criteria for cadaveric transplantation, particularly since LDLT recipients may need an urgent cadaveric liver transplant if the live graft fails. Nevertheless, debate continues over whether LDLT should be offered to recipients who do not meet the accepted criteria for cadaveric organ donation [20, 85-87].

There is doubt surrounding the ethics of unrelated live liver graft donation. Live organ donation was once restricted to donors with a genetic link to the recipient, but improvements in immunosuppression have extended this option to unrelated individuals who have an emotional relationship with the recipient [75]. The proportion of live grafts that come from so called Good Samaritan donations, where the donor is unrelated to the recipient, is growing, and there is concern that this trend will result in the potentially unethical practice of accepting live liver grafts from donors who have no emotional attachment to the recipient whatsoever. However, this concern is partly underpinned by the erroneous assumption that the quality of a relationship between two individuals is related to their degree of genetic linkage [83]. Ultimately, it is still unclear if restrictions should be placed on who can become a live donor, and whose responsibility it is to make such a decision [83].

The ethical issues surrounding LDLT include the need for: autonomy of the donor and the recipient; an environment where the donor is not subject to coercion; and informed donor consent supported by a true estimate of the utility of LDLT and donor complication rates, and the identification of any future physical and financial risks for the donor [14, 81]. The ethical challenges of performing LDLT when the recipient has fulminant liver failure are greater because the urgent nature of the procedure makes it more difficult to complete the screening and education of the donor. Thus, it is almost impossible for the donor to make a properly informed decision that is free from coercion [14, 20, 85]. In addition, there are no standard protocols for the preoperative evaluation of potential donors, and postoperative donor follow-up is generally ad hoc and rarely includes psychosocial evaluation or support [78, 79]. This may need further examination since it has been noted that 20% to 30% of children demonstrate psychosocial problems after receiving a liver transplant. Moreover, the siblings and parents of graft recipients, as well as the partners of LDLT donors, report immense distress and disruption of family activities [88, 89].

There is a significant learning curve associated with performing LDLT and procedure volume is positively correlated with patient outcome [90]. It is generally agreed that LDLT should not be performed at centres conducting fewer than 20 liver transplants per year and that any surgical team undertaking LDLT should be experienced in hepatobiliary surgery, as well as cadaveric whole organ and split liver transplantation [14, 17, 54, 91].

The Future of Adult to Child LDLT

Approximately two in every 10,000 children born will eventually require a liver within the first few years of life [58]. It is unlikely that LDLT will solve the chronic shortage of liver grafts since up to 75% of recipients do not have a suitable donor [92]. However, if pediatric liver transplantation represents 10% to 15% of the demand for liver grafts, and 15% to 25% of donor livers are suitable for splitting, it is possible that the full application of SLT would provide a surfeit of donor organs for the pediatric population [16, 35]. Thus, while LDLT is clearly not the solution to the cadaveric liver shortage, there is the expectation that waiting list mortality for children can be expunged with the judicious application of LDLT and SLT [54]. However, 12.1 liver transplants were performed per million Canadians in 2002, which is much lower than the US rate of 18.3 and is largely due to the lower cadaveric donation rates in Canada [31].

In an ideal world, it would not be necessary to put a healthy person's life at risk for organ donation. Thus, it is important to continue initiatives aimed at increasing consent rates for cadaveric organ donation in order to decrease the need for LDLT. Future developments in transplant surgery may expand the use of domino transplants and grafts from non-beating heart or marginal donors, such as those who are obese [19, 20, 93]. In the long-term, tissue engineering, hepatocyte and stem cell transplantation, gene therapy, bioartificial liver, extracorporeal liver support, and xenotransplantation may offer alternative treatments for liver failure that could obviate the need for LDLT [14, 19, 21, 46, 94]. Strategies aimed at increasing the function of segmental grafts, promoting early graft regeneration, and reducing the likelihood of graft rejection, ischemic or hyperperfusion injury, and disease recurrence may also encourage the use of SLT [33, 39].

CONCLUSION

Despite its popularity, the evidence base for LDLT is incomplete. The current limited evidence suggests that LDLT is superior to all forms of cadaveric liver transplantation in children younger than two years of age. However, the safety and efficacy of LDLT was equivalent to, and in some cases worse than, SLT and whole liver cadaveric donation in older children. Thus, it is reasonable to assume that LDLT would not be performed at centres where there is an abundant supply of cadaveric organs. The expansion of SLT is likely to diminish the need for LDLT and increase scrutiny of the ethics surrounding the use of LDLT in pediatric liver

transplantation. Despite its limitations, LDLT is a life saving procedure for some individuals where alternative transplant options are not available, such as for very small children or for elective patients whose condition is likely to deteriorate before a cadaveric graft becomes available. Future initiatives in LDLT must aim to achieve minimal morbidity and zero mortality for donors. Programs performing LDLT must adhere to an extremely high standard of care that includes standard protocols for preoperative evaluation of potential donors and postoperative follow-up of both donors and recipients, as well as strong psychosocial evaluation and support programs.